REMARKS

Claims 4-7, 9, and 11-17 are pending.

Priority

The Examiner asserts that the priority date for this application is August 24, 2000. Applicants reiterate that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to U.S. Application 09/380137 filed 8/25/99, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. §119 to U.S. Provisional Application 60/090688 filed 6/25/1998.

Information Disclosure Statement

The Examiner indicates that the BLAST results submitted with the previous IDS have not been considered because there is no alignment provided, nor is there an indication of the percent identity between the claimed sequence and the reference sequences.

Applicants provide alignments and indications of the percent identity with the accompanying Information Disclosure Statement.

Utility

The Examiner asserts that the *Juicy Whip v. Orange Bang* decision is not relevant. According to the Examiner, the art recognizes that mRNA expression level is not well correlated with protein expression level. Haynes et al. is cited in support of the Examiner's position.

The Examiner also asserts that Applicants' disclosure of a change in levels of a fragment of the nucleic acid encoding SEQ ID NO:48, wherein the levels are increased in some tumors and decreased in others, is not sufficient to make the protein encoded by the full-length nucleic acid useful.

The Examiner also asserts that since PRO994 expression increases in one tumor and decreases in another, its expression level cannot be considered as a marker for the presence or absence of a tumor. In addition, the Examiner asserts that because the correlation between

expression of the nucleic acid and the protein is poor, data as to the expression of nucleic acids do not bear on the utility of the proteins and that further research and experimentation are required to find out whether the claimed polypeptides are useful as asserted.

The Examiner asserts that *In re Langer, In re Jolles, In re Irons, Sichert, Raytheon v. Rope, In re Oetiker, Fujikawa v. Wattanasin,* and *Cross v. Iizuka* are not relevant to the present application.

The Examiner also asserts that the previously submitted Grimaldi, Polakis and Ashkenazi Declarations are insufficient. Hu is cited as cautioning researchers from drawing conclusions based on small changes in transcript expression levels. Tokunaga et al. is cited as teaching that qualitative analysis of gene expression in cancer tissue using RT-PCR is not sufficient, rather quantitative analysis must also be used and that for clinical applications much further research is needed. Chen et al. is cited as teaching that of 165 nucleic acid-protein pairs examined, only a small subset showed a significant correlation and that overall there is not a significant correlation between gene expression and protein expression in cancer. Haynes is cited as showing that mRNA expression level is not well correlated with protein expression level.

The statement in Meric et al. that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability" is cited as supporting the Examiner's position that mRNA levels do not correlate with polypeptide levels.

Utility – Legal Standard

As previously noted, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly

is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics,**

> **or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

As previously noted, an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable

correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic or therapeutic tools for cancer, particularly stomach tumor or rectum tumor. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively;

2. Applicants assert that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding **change** in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO994 polypeptide is increased in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively, it is likely that the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively;

4. Proteins which are differentially expressed in certain tumors are useful as diagnostic and therapeutic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO asserts that the claimed polypeptides lack utility because the mRNA encoding the PRO994 polypeptide is more highly expressed in rectum tumor (i.e upregulated in rectum tumor) and is expressed less in stomach tumor than in normal stomach tissue (i.e. downregulated in stomach tumor).

2. The PTO asserts that one cannot draw conclusions based on small changes in mRNA levels.

3. The PTO also asserts that the literature demonstrates that mRNA levels can vary without a change in protein level.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants maintain that, in general, differential expression of an mRNA correlates with differential expression of the encoded polypeptide. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As

stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO994 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Claims 4-17 were rejected on the assertion that the claimed subject matter lacks utility. The Examiner asserts that since PRO994 expression increases in one tumor and decreases in another, its expression level cannot be considered as a marker for the presence or absence of a tumor. According to the Examiner, there is no correlation between the level of PRO994-encoding nucleic acid and the presence or absence of a tumor.

As previously noted, the data in Example 18 demonstrates that the mRNA encoding PRO994 is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue. In support of this position, Applicants have previously submitted a copy of a first declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (first Grimaldi Declaration, Paragraph 7).

As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (first Grimaldi Declaration, Paragraph 7, emphasis added). The data presented in Example 18 show that the gene encoding PRO994 is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. As the first Grimaldi

declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic or therapeutic tools.

Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept the statements in Mr. Grimaldi's Declaration.

With respect to the Examiner's position that the claimed polypeptides lack utility because the nucleic acids encoding them are overexpressed in rectum tumor and underexpressed in stomach tumor, Applicants maintain that, as discussed above, the data showing these expression patterns are reliable. Furthermore Applicants note that one using the claimed polypeptides as a diagnostic tool would know whether the sample being assessed originates from stomach or from rectum. Accordingly, one can readily assess whether the claimed polypeptides are under-expressed in a sample originating from stomach (indicating the individual from whom the sample was taken may have stomach cancer) or whether the claimed polypeptides are over-expressed in a sample originating from rectum (indicating that the individual from whom the sample was taken may have a rectal tumor). In view of the foregoing, Applicants maintain that the claimed polypeptides can be used as a marker for the presence or absence of stomach tumor or rectum tumor.

The Examiner asserts that the Declaration by Mr. Grimaldi is insufficient to overcome the rejections. According to the Examiner, the claims are drawn to polypeptides encoded by SEQ ID NO:47 but the specification indicates that oligonucleotide probes were designed to amplify a portion of the DNA. According to the Examiner, what was analyzed was the expression level of

a part of SEQ ID NO:47, not the entire sequence. The Examiner maintains that the data presented are narrow, in that they deal with a fragment of SEQ ID NO:47 200-600 bp in length while the claims are drawn to the full-length protein of SEQ ID NO:48 or fragments or variants thereof.

In addition, the Examiner asserts that the data presented are subjective in nature and not objective. In particular, the Examiner asserts that there is no indication how the expression levels were scored, nor is there any indication of what differentiates either a + or - sample from an intermediate (+/-) sample. The Examiner also asserts that there is no indication that the data are repeatable, as the experiments seem to have been performed once on a single sample. According to the Examiner, it is likely that the variability seen is not significant and would be expected by random variation alone. The Examiner maintains that this is corroborated by the fact that PRO994 is up-regulated in rectum tumor but down-regulated in stomach tumor.

Applicants maintain that the levels of the 200-600bp fragments detected in the semi-quantitative amplification experiments described in Example 18 are indicative of the levels of the full length transcripts. In particular, Applicants maintain that the Examiner has provided no basis for asserting that the level of an amplification product generated using primers within a portion of a full length transcript is not representative of the level of the full length transcript. Applicants maintain that semi-quantitative PCR is a well established technique for assessing the level of transcript within a sample and the Examiner has not cited any references contrary to this position. With respect to the Examiner's assertion that the data are subjective in nature, Applicants maintain that, as discussed above, the first Declaration of J. Christopher Grimaldi establishes that the data in Example 18 is reliable and that a positive score in the quantitative PCR analysis of Example 18 indicates that there was <u>at least</u> a two-fold difference in expression. Furthermore, one skilled in the art using the claimed polypeptides as a diagnostic tool would know whether the sample being assessed originates from stomach or from rectum. Accordingly, one can readily assess whether the claimed polypeptides are under-expressed in a sample originating from stomach (indicating the individual from whom the sample was taken may have stomach cancer) or whether the claimed polypeptides are over-expressed in a sample originating from rectum (indicating that the individual from whom the sample was taken may have a rectal tumor).

Hu et al. is cited as cautioning researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The Examiner asserts that Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, the Examiner acknowledges that Hu et al. indicates that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

As previously noted, in Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and

reflect nothing regarding the ability of a polypeptide that is 2-fold or more differentially expressed in tumors to be used as a diagnostic.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer or their corresponding proteins cannot serve as a molecular marker of cancer.

Tokunaga et al. is cited as teaching that qualitative analysis of gene expression in cancer tissue using RT -PCR is not sufficient and that quantitative analysis must also be used. The Examiner asserts that Tokunaga et al. also teaches that for clinical applications much further research is needed.

Tokunaga is concerned about possible false positive results which might be obtained when assessing the expression of the CK18 gene to evaluate cancer metastasis. Such false positives may occur due to the sensitivity of PCR, which may generate a CK18 amplification product even if the level of CK18 mRNA is below that of physiological significance. Such concerns are not applicable to experiments such as those described in Example 18. In contrast to the analyses performed by Tokunaga where the presence or absence of CK18 mRNA or the specific amount of CK18 mrNA is being assessed, in the experiments described in Example 18 of the present specification the relative levels of mRNA in normal tissue and tumor tissue are compared. In such situations, where one is looking for relative differences rather than the presence or absence of an amplification product or the specific amount of an amplification product, qualitative analyses are sufficient. As noted above, Dr. Grimaldi's Declaration provides that "The precise levels of gene expression are irrelevant; what matters is that there is a relative

difference in expression between normal tissue and tumor tissue." (first Grimaldi Declaration, Paragraph 7). Accordingly, Applicants maintain that the semi-quantitative analysis described in Example 18 provides a reliable indication of the differential expression of the PRO994 mRNA.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants submit that they have established for the record that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO994 polypeptide in stomach tumor and rectum tumor, it is more likely than not that the PRO994 polypeptide is also differentially expressed.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 2). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and previously submitted therewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels*

> *are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (previously submitted as Exhibit 4) and (4th ed. 2002) (previously submitted as Exhibit 5)). Figure 9-2 of Exhibit 4 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 4 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 4 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 4 at 453 (emphasis added). Thus, as established in Exhibit 4, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 5, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 5 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 5 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 5 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for

regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 5 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (previously submitted as Exhibit 6) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, previously submitted as Exhibit 7. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Exhibit 7 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 7 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 7 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted previously as Exhibit 8, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The Examiner asserts that the second declaration submitted by Dr. Grimaldi is insufficient to overcome the rejections because the facts presented are not germane to the rejection at issue. According to the Examiner, in paragraph 5, Dr. Grimaldi asserts that there are often correlations between expression of nucleic acid and of protein. The Examiner maintains that there is no such correlation. As discussed above, Applicants maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed.

The Examiner asserts that the Declaration of Dr. Polakis is unpersuasive. According to the Examiner, the specification discloses that the expression of a part of the nucleic acid encoding SEQ ID NO:47 is not correlated with cancer because it is increased in cancer in one tissue and decreased in another. The Examiner also asserts that the declaration does not provide data such that the Examiner can independently draw conclusions. The Examiner maintains that the declaration is not on point to the claimed sequence as it does not state that these successes are in using cancer diagnostics with the instantly-claimed sequences. According to the Examiner, there is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.

As discussed above, the levels of the amplification products obtained in the experiments of Example 18 are indicative of the levels of the full length transcript. Furthermore, as discussed above, Applicants maintain that they have provided reliable data showing that PRO994 mRNA is differentially expressed in stomach tumor and rectum tumor. As discussed above, the references cited by the Examiner do not contravene Applicants' position that, in general, differential expression of mRNA leads to differential expression of the encoded polypeptide. Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Dr. Polakis is an expert in the field and conducted or supervised the experiments at issue. Furthermore, Dr. Polakis' statements are based on his experience in over 20 years of research. Furthermore, Applicants maintain that Dr. Polakis' conclusion that it is a central dogma in

molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein is supported by the references previously submitted by Applicants and discussed above.

Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Dr. Polakis based his analysis. Dr. Polakis has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept the statements in Dr. Polakis' Declaration.

The Examiner asserts that the Ashkenazi Declaration is not persuasive. According to the Examiner, the data presented in the specification were from an RT-PCR assay, not a gene amplification assay. The Examiner asserts that the fragment of the nucleic acid with SEQ ID NO:47 has not been found to be correlated with cancer expression. The Examiner further asserts that there is no evidence as to whether the gene products (i.e. the polypeptide) are over-expressed or not and that considerable further research is required to determine whether the gene product is overexpressed.

As discussed above, the first Declaration of J. Christopher Grimaldi establishes that the data in Example 18 is reliable. In addition, Applicants maintain that the levels of the 200-600bp fragments detected in the semi-quantitative amplification experiments described in Example 18 are indicative of the levels of the full length transcripts. Furthermore, as discussed above, one skilled in the art using the claimed polypeptides as a diagnostic tool would know whether the sample being assessed originates from stomach or from rectum. Accordingly, one can readily assess whether the claimed polypeptides are under-expressed in a sample originating from stomach (indicating the individual from whom the sample was taken may have stomach cancer) or whether the claimed polypeptides are over-expressed in a sample originating from rectum (indicating that the individual from whom the sample was taken may have a rectal tumor). As

discussed above, Applicants note that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed.

Haynes et al. is cited as teaching that mRNA levels can vary up to 40-fold without a change in protein level. Haynes does not contradict the utility of the polypeptides encompassed by the instant claims. Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the Examiner were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." Id. However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured.

The variation referred to by Haynes and cited by the Examiner, does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. Exact levels of expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO994 mRNA has been shown in Example 18 of the specification to be more highly expressed in normal stomach or rectum tumor compared to stomach tumor or normal rectum tissue respectively, the variability identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

The Examiner also asserts that Applicants' remarks indicate that other controls can act later in the pathway from RNA to protein. Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and

declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes.

As previously noted, Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

As previously noted, in Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added).

As previously noted, Lewin states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Thus, it is clear from Lewin that protein expression is predominantly regulated at the point of transcription initiation.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship

between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed polypeptides because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately

predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the

authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not that there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed herein, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between **changes** in mRNA levels and **changes** in protein levels for a particular gene.

The statement in Meric et al. that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability" is cited as supporting the Examiner's position that there is no correlation between mRNA levels and protein levels. As noted above, Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and Declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes. Meric supports this assertion because "[t]he **fundamental principle** of molecular therapeutics in cancer is to exploit the **differences** in gene expression between cancer cells and normal cells." Meric *et al.* at 971 (emphasis added). The only reason mRNA is of any interest in studying the mechanism of cancer formation and growth is because mRNA encodes protein. If there were no general correlation between differences in mRNA and differences in protein, there would be no reason to study changes in mRNA.

The Examiner asserts that the *Juicy Whip v. Orange Bang* decision is not relevant because in the instant case the PTO has not made a 101 rejection because of an intent to deceive but rather because the invention itself has no utility. Applicants appreciate that the PTO has not based the current utility rejection on an intent to deceive. However, Applicants maintain that *Juicy Whip* is pertinent because it establishes that "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992). Like the device at issue in *Juicy Whip*, the claimed polypeptides are not "totally incapable of achieving a useful result." Accordingly, Applicants maintain that the utility rejection should be withdrawn.

The Examiner asserts that *In re Langer* is distinguishable from the present situation because in the present case, the Office has not required clinical testing. According to the Examiner, in the present case there is sufficient reason to question the statement of utility. The Examiner asserts that the claimed polypeptides are not clearly useful as either diagnostics or therapeutics for cancer because there is not evidence of a correlation between the expression level of the protein and the presence or absence of a tumor.

As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the polypeptides recognized by the claimed polypeptides are differentially expressed in stomach tumors and rectum tumors. Accordingly, Applicants maintain that *In re Langer* is applicable to the present application.

The Examiner asserts that in *In re Jolles* the issue was whether data from an art-recognized animal model could be considered predictive of results in humans but that this is not an issue in the instant case because the data are from human tissue samples. However, the Examiner asserts that in the present situation there is no evidence of a correlation of protein levels with cancer. As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the claimed polypeptides are differentially expressed in stomach tumors and rectum tumors. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed. Thus, just as the animal data at issue in *In re Jolles* was found to be sufficiently predictive of results in humans to satisfy the utility requirement, Applicants maintain that differential expression of the polynucleotide

encoding the claimed polypeptides is sufficiently predictive of differential expression of the encoded polypeptide to satisfy the utility requirement. Accordingly, Applicants maintain that *In re Jolles* is applicable to the present application.

The Examiner asserts that *In re Irons* is also not relevant to the present situation because the only data of record are drawn to the nucleic acid but the claims are drawn to protein. The Examiner also maintains that there is no evidence of record indicating a statistically significant result at either the nucleic acid or the protein level. As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the claimed polypeptides are differentially expressed in stomach tumors and rectum tumors. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed. Accordingly, Applicants maintain that *In re Irons* is applicable to the present application.

The Examiner asserts that the *Sichert* decision is not relevant to the present situation because the Applicant has not shown any clinical studies as was done in *Sichert*. Applicants maintain that, as noted in *In re Sichert*, an asserted utility which is not inherently incredible or unbelievable should be accepted by the PTO. As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the polypeptides recognized by the claimed polypeptides are differentially expressed in stomach tumors and rectum tumors. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed. Applicants maintain that, like the situation in *In re Sichert*, the asserted utility is neither incredible nor unbelievable. Accordingly, the PTO should not assert that the claimed polypeptides lack utility.

The Examiner asserts that in *Raytheon v. Roper,* utility was found by the Federal Circuit when a lack of utility had been found by a lower court but that this was due not to the sufficiency of the evidence presented, but rather because the Federal Circuit ruled that the claims in question had been interpreted erroneously. According to the Examiner, in the present situation there does not appear to be a question as to how the pending claims are being interpreted. Rather, the Examiner maintains that utility is lacking because there is no correlation between SEQ ID NO:48 expression and the presence or absence of cancer. As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the claimed polypeptides are

differentially expressed in stomach tumors and rectum tumors. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed. Accordingly, Applicants maintain that *In re Irons* is applicable to the present application.

According to the Examiner, *In re Oetiker* is not relevant because it relates to obviousness rather than utility. Applicants note that *In re Oetiker* was cited for the proposition that the Examiner bears the burden of presenting a *prima facie* case of unpatentability to support a rejection on any basis, including utility. As discussed herein, Applicants maintain that the Examiner has not satisfied that burden with respect to the claimed polypeptides.

The Examiner asserts that in *Fujikawa v. Wattanasin*, the court ruled that test results need not absolutely prove the asserted utility but that in the present case, there is not a correlation between the instantly-claimed product (the polypeptide of SEQ ID NO:48) and any disease or condition. As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the claimed polypeptides are differentially expressed in stomach tumors and rectum tumors. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differenctially expressed. Polypeptides which are differentially expressed in tumors are useful as diagnostic or therapeutic tools. Accordingly, Applicants maintain that the claimed polypeptides possess utility.

With respect to *Cross v. Iizuka*, the Examiner asserts that the specification does not disclose the results of any tests, *in vitro* or *in vivo,* that support the utility of the polypeptide of SEQ ID NO:48. As discussed above, Applicants have provided reliable data showing that the polynucleotides encoding the claimed polypeptides are differentially expressed in stomach tumors and rectum tumors. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed. Polypeptides which are differentially expressed in tumors are useful as diagnostic or therapeutic tools. Accordingly, Applicants maintain that the claimed polypeptides possess utility.

The Examiner asserts that proteins 100% identical to SEQ ID NO:48 are not useful and that, accordingly, proteins which are not identical to SEQ ID NO:48 are also not useful. According to the Examiner, since the requirement of new claims 14 -17 is that the fragment or

variant be capable of detecting SEQ ID NO:48, and there is no use for SEQ ID NO:48, there would be no use for the antibodies which could be raised against the variant.

Applicants maintain that, as discussed above, the polypeptide of SEQ ID NO: 48 is useful and that, accordingly, fragments or variants which can be used to generate antibodies which can detect the polypeptide of SEQ ID NO: 48 are useful.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants maintain that the claimed polynucleotides possess a specific utility. Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO994 gene in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the mRNA for the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. These data are strong evidence that the PRO1994 polypeptide is associated with stomach tumor and rectum tumor. Thus, Applicants submit that they have provided evidence associating the PRO994 gene and polypeptide with a specific disease. The asserted utility of the claimed polypeptides as a diagnostic or therapeutic tool for cancer, particularly stomach tumor and rectum tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has challenged the reliability of the evidence reported in Example 18 and asserts that the claimed polypeptides lack utility because they are more highly expressed in rectum tumor (i.e upregulated in rectum tumor) and expressed less in stomach tumor than in normal stomach tissue (i.e. downregulated in stomach tumor). The PTO also asserts that it has provided numerous references which demonstrate that one cannot draw conclusions based on small changes in mRNA levels. The Examiner also asserts that the literature demonstrates that mRNA levels can vary without a change in protein level.

Applicants have previously provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. Applicants also maintain that one skilled in the art can readily determine whether the claimed polypeptides are overexpressed in a sample from rectum tissue or underexpressed in a sample from stomach tissue. Applicants have demonstrated that the Hu et al., Haynes et al. and Tokunaga et al. references cited by the Examiner do not contravene the utility of the claimed polypeptides. Applicants further maintain that, in general, polypeptides encoded by differentially expressed mRNAs are also differentially expressed. One of skill in the art recognizes that polypeptides which are differentially expressed in certain cancers have utility as diagnostic or therapeutic tools for cancer. Applicants note that the claimed utility is specific because differential expression in stomach tumor or rectum tumor is not a characteristic of polypeptides in general.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic or therapeutic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Enablement

Claims 4-17 were rejected under 35 U.S.C. 112 on the assertion that, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention. According to the Examiner, even if utility were found for PRO994 (SEQ ID NO:48), enablement would still not be commensurate in scope with claims 4-5, and 12-13 because the specification does not reasonably provide enablement for fragments or variants 95% or 99% identical to SEQ ID NO:48 which are more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue, or for fragments or variants encoded by polynucleotides with said expression profile. The Examiner asserts that the specification does not provide guidance as to which regions of the protein are necessary for the fragments or variants to have the claimed expression pattern. The Examiner acknowledges that where a protein is known to have a particular activity it is inappropriate to make a rejection to claims reciting variants having 95% identity and the same activity. However, the Examiner asserts that, in the instant case, no activity has been disclosed for the claimed protein of SEQ ID NO:48.

The claims recite that the claimed polypeptides are more highly expressed in normal stomach or rectum tumor compared to stomach tumor or normal rectum respectively, have a specified level of homology to SEQ ID NO: 48, or can be used to generate antibodies which can be used to specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples. As discussed in more detail below, Applicants maintain that, in view of the combination of the foregoing functional limitations, there is not substantial variability within the species which fall within the scope of the claim. In addition, Applicants note that the claimed invention pertains to the field of recombinant DNA/protein technology and that the level of skill in this field is very high. Variant polypeptides and variant polynucleotides are described in the specification at paragraphs [0199]-[0220]. Furthermore, Applicants maintain that the determination of whether a polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively involves routine methodology such as Western blotting. The implementation of routine techniques does not constitute undue experimentation. (See *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

With respect to the Examiner's assertion that no activity has been disclosed for the polypeptide of SEQ ID NO: 48, as previously noted, in Example 14 of the Written Description Training Materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the claimed polypeptides have very high sequence homology to the disclosed sequences and share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in stomach tissue or rectum tissue, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach tissue or rectum tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation. Again, although Applicants realize that Example 14 relates to written description rather than enablement, Applicants maintain that, in view of the fact that the claimed polypeptides are adequately described and the fact that the use of these polypeptides as diagnostic or therapeutic tools involves routine methodology, one skilled in the art would readily be able to make and use the claimed polypeptides.

The Examiner also asserts that the specification does not reasonably provide enablement for extracellular domains at residues 32-49 or 111-190 of SEQ ID NO:48 or SEQ ID NO:74. According to the Examiner, Figure 48 of the specification indicates the location of four transmembrane domains, but neither the figure nor the specification discloses which regions of the protein are intracellular or extracellular. The Examiner asserts that if the N-terminal region of the protein is intracellular, then the regions between residues 32-49 and 111-190 are in fact extracellular but that if the N-terminal region is extracellular, then residues 1-9, 73-86, and

214-229 are extracellular. According to the Examiner, the specification does not disclose which regions are intracellular and which are extracellular.

Applicants have deleted the terminology "extracellular domain" from the claims. Applicants maintain that Figure 48 discloses the positions of transmembrane domains between amino acids 10-31, 50-72, 87-110 and 191-213 of SEQ ID NO: 48. The demarcation of these regions of the protein also demarcates the intervening amino acids at positions 32-49 and 111-190 of SEQ ID NO: 108. Accordingly, the recitation of these portions of the polypeptide does not constitute new matter.

The Examiner asserts that Claims 14 and 15 recite SEQ ID NO:74 in part (d) and that the specification discloses that SEQ ID NO:74 has a single transmembrane domain at residues 291-310. According to the Examiner, a skilled artisan could not make a variant of SEQ ID NO:74 with the assurance that the extracellular domains are from residues 32-49 and 111-190 because the specification does not disclose which end of SEQ ID NO:74 is intracellular and which end is extracellular. The Examiner also asserts that sequences at least 95% identical to SEQ ID NO:74 cannot be used to generate antibodies that recognize SEQ ID NO:48.

Applicants have amended the claims to refer to SEQ ID NO: 48 rather than SEQ ID NO: 74. Accordingly, the foregoing rejections are moot.

Written Description

Claims 4-5 and 12-13 were rejected under 35 U.S.C. 112 on the assertion that they fail to comply with the written description requirement. The Examiner asserts that the specification does not show which regions of SEQ ID NO:48 are required for the resulting variants or fragments to have the instantly-claimed activity. According to the Examiner, the specification discloses only the full-length protein (SEQ ID NO:48) and not any variants or fragments. As discussed above, the Examiner distinguishes Example 14 of the training materials on the assertion that there is no disclosure that SEQ ID NO:48 has the claimed expression profile.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re*

Kaslow, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% amino acid sequence identity to several polypeptides related to SEQ ID NO: 48, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal stomach tissue or rectum compared to stomach tumor or normal rectum tissue respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach tissue or rectum compared to stomach tumor or normal rectum tissue respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples."

As discussed in the response to the previous Office Action, Applicants maintain that there is not substantial variation within the species which fall within the scope of the amended claims,

which require at least 95% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 48. Applicants note that the pending claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in lung tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples. Like Example 14, the genus of polypeptides that have at least 95% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, with respect to the Examiner's concern that there is no disclosure that SEQ ID NO: 48 has the claimed expression profile, as discussed above, Applicants have provided reliable data to demonstrate that the polypeptide of SEQ ID NO: 48 is differentially expressed.

With respect to the Examiner's concern regarding fragments of SEQ ID NO: 48, Applicants maintain that the disclosure of the full length sequence necessarily provides written description of fragments within the full length sequence.

Claims 14 and 15 recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody." According to the Examiner, Applicants have not shown which regions of the peptide must be conserved in order to raise antibodies which can detect SEQ ID NO:48.

Example 16 of the Written Description Training Materials indicates that antibodies which bind to antigen X are adequately described by a specification which provides the sequence of

antigen X but which does not contain examples demonstrating the production of antibodies against antigen X. Example 16 indicates that production of antibodies against a well-characterized antigen is conventional. In fact, Applicants maintain that one of skill in the art can readily generate antibodies against the claimed polypeptides or determine whether the claimed polypeptides are able to generate antibodies which can detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples using routine methodology such as that described in Paragraphs [361]-[390] of the specification. Applicants maintain that since Example 16 demonstrates that the written description requirement is satisfied for antibodies against a well-characterized polypeptide, it must also be satisfied for polypeptides capable of inducing antibodies, as claimed in the present application.

The Examiner asserts that Claims 14 and 15 are drawn to fragments at least 95% identical to SEQ ID NO:74, which can be used to raise antibodies against SEQ ID NO:48. According to the Examiner, Applicant has not demonstrated which regions of SEQ ID NO:74 could be used to raise antibodies that recognize SEQ ID NO:48.

Applicants have amended the claims to recite SEQ ID NO: 48 rather than SEQ ID NO: 74. Accordingly, Applicants maintain that the foregoing rejections are moot.

Claim Objections

Claims 14 and 15 were objected to because part (d) of both claims recites "SEQ ID NO:74" while the remainder of the instant claims are drawn to SEQ ID NO:48.

Applicants have amended the claims to recite SEQ ID NO: 48 rather than SEQ ID NO: 74. Accordingly, Applicants maintain that the foregoing objection is moot.

New Matter

As noted above, Claims 4-11 and 14-15 were rejected on the assertion that, since there was no disclosure of which regions were intracellular or extracellular in the application, identification of such regions is deemed to be new matter.

As discussed above, Applicants have deleted the terminology "extracellular domain" from the claims. Applicants maintain that Figure 48 discloses the positions of transmembrane domains between amino acids 10-31, 50-72, 87-110 and 191-213 of SEQ ID NO: 48. The demarcation of these regions of the protein also demarcates the intervening amino acids at

positions 32-49 and 111-190 of SEQ ID NO: 108. Accordingly, the recitation of these portions of the polypeptide does not constitute new matter.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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